

Remarks

Claims 23-36 are pending in the subject application. By this Amendment, Applicants have canceled claims 27-30, amended claims 23-26, 31 and 33 and added new claims 36-37. Support for the amendments and new claims can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 23-26 and 31-37 are currently before the Examiner (with claims 23-26 and 36-37 reading on the elected species). Favorable consideration of the pending claims is respectfully requested.

Applicants gratefully acknowledge the Examiner's withdrawal of the rejection under 35 U.S.C. § 102(b) (over Tsuhako *et al.*) and the provisional double patenting rejection.

Claim 23 is objected to because of informalities. The Examiner indicates that conjunctions are missing before the last subsections in claim 23. Applicants gratefully acknowledge the Examiner's careful review of the claims. Claims 23 and 33 have been amended to include the conjunction "or" after the subsections within the claims. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claims 23 and 26 are rejected under 35 U.S.C. § 103(a) as obvious over Fox *et al.* (2002) in view of Patani *et al.* (1996) and in view of Parvin *et al.* (1969). In addition, claims 23 and 26 are rejected under 35 U.S.C. § 103(a) as obvious over Fox *et al.* (2002) in view of Patani *et al.* (1996) and in view of Parvin *et al.* (1969) and further in view of Sicard *et al.* (2000) and Cox *et al.* (1997). The Office Action claims that Fox *et al.* disclose the pyrophosphate-containing compound HDMAPP as a metabolic intermediate in the synthesis of IPP for the study of the metabolic process and disclose the pyrophosphate-containing compound HDMAPP in a solvent comprising aqueous ammonium carbonate buffer and isopropanol, which is a pharmaceutically acceptable carrier such as for topical applications. The Office Action states that Patani *et al.* teach bioisosterism is a well known approach to influence the metabolism of a compound and teach oxygen and nitrogen are well known isosteres. The Office Action also states that Patani *et al.* teach the monovalent interchange of amino and hydroxyl groups is well known as a classical bioisostere and the oxygen and NH are well known as a classical divalent bioisosteres as well. The Office Action indicates that Parvin *et al.* teach phosphate and phosphoramidate are known in the art of biochemical metabolic studies as substrates of the same

enzyme activity, meaning that they are known as bioisostERICALLY equivalent. The Office Action asserts that Sicard *et al.* teach that one or more of the metabolic intermediates of the pathway disclosed in Fox *et al.* exhibit immunological stimulatory activity. The Office Action further states that Sicard *et al.* teach IPP produced by the metabolic pathway is also an antigen. Finally, the Office Action notes that Sicard *et al.* teach it is desired to increase the immune response of the specific metabolic intermediates. The Office Action alleges that Cox *et al.* teach adjuvants are well known in the art to enhance the immune response of a compound by a number of different modes of action. Applicants respectfully assert that the claimed invention is not obvious over the cited references. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

The Examiner asserts that Fox *et al.* disclose the compound HDMAPP and that Patani *et al.* teach bioisosterism is a well known approach to influence the metabolism of a compound. The Examiner thus asserts that it would have been obvious to one of ordinary skill in the art at the time of the invention to combine Fox *et al.* in view of Patani *et al.* and in view of Parvin *et al.* to obtain the claimed compounds. Applicants respectfully disagree.

To render a claim obvious, there must be “an apparent reason to combine the known elements in the fashion claimed” by the applicant, “other than the hindsight gleaned from the invention itself.” *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985), *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 41 (2007). “A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 41 (2007). In addition, a reasonable expectation of success is required to establish a *prima facie* case of obviousness. M.P.E.P. 2143.02. “An invention would not have been obvious to try when the inventor would have to try all possibilities in a field unreduced by direction of the prior art, . . . where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.” *Bayer Schering Pharma AG. v. Barr Lab., Inc.*, 91 USPQ2d 1565, 72-73 (Fed. Cir. 2009), *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988).

It is acknowledged that Fox *et al.* teach the compound HDMAPP. However, absent the teachings of the instant application, it is unclear why one of ordinary skill in the art would have

selected the phosphoester oxygen for substitution with an amide group as opposed to any other atom within the HDMAPP structure. Indeed, Sicard *et al.* only teach isopentenyl pyrophosphate (IPP) compounds containing a pyrophosphate group as having activity for stimulating  $\gamma\delta$  T cell. Thus, there would have been no motivation to substitute a phosphoester oxygen atom in an IPP compound with another atom.

While Patani *et al.* is directed to a rational approach to drug design, it is unclear that the teachings of Patani *et al.* would have been interpreted as urged in the Office Action. For example, Applicants note that the substituted atom in HDMAPP is an oxygen atom that forms a phosphoester bond with a carbon atom. Patani *et al.*, in the divalent isostere section at page 3155, discuss divalent isosteres that involve atoms having a double bond (C=C, C=N or C=O) or the alteration of two single bonds (C-C-C, C-NH-C, C-O-C or C-S-C). Notably absent from that discussion is a bond such as that which distinguishes N-HDMAPP from HDMAPP, namely C-NH-P as compared to C-O-P. Thus, it is unclear, on the basis of the teachings of Patani *et al.*, that bioisosterism applies to compounds having a phosphoester linkage and that the substitution of an NH group for the oxygen in the phosphoester group is a recognized form of bioisosterism. Applicants also note that the Office Action argues that Patani *et al.* teach that the substitution of an amine group for a hydroxyl group is a recognized form of bioisosterism; however, no such substitution has been made in the claimed compound.

In that same section of Patani *et al.*, it is stated "*The bond angle or the conformation associated with the use of these divalent biososteres may be an important factor associated with retention of biological activity*" (page 3156, left column first paragraph). Tables 19 and 20 (of Patani *et al.*) provide comparison between bioisosteric compounds and their biological activity. In the case of Tables 19 and 20, the "O" bioisosteres are much more active than S, CH<sub>2</sub> or NH bioisosteres. In the case of phosphoantigens (biological molecules such as that claimed in this application), the substitution of a phosphoester oxygen atom with a CH<sub>2</sub> group has been demonstrated to alter the biological activity of a  $\gamma\delta$  T cell agonist such that it becomes a  $\gamma\delta$  T cell antagonist. BrHPP (the O bioisostere) is a  $\gamma\delta$  T cell activator (see U.S. Patent No. 7,399,756) whereas the CH<sub>2</sub> bioisostere of BrHPP antagonizes  $\gamma\delta$  T cell activity (see U.S. Patent No. 6,624,151). Thus, it is clear that the substitution of one atom for another within the same compound can lead to

compounds that are antagonistic in function and that the effects of bioisosteric substitution can be unpredictable.

As shown in Figure 1, NHDMAAPP (species X), as claimed in the instant application, has a far more potent  $\gamma\delta$  T cell stimulating effect as compared to the HDMAPP compound. Indeed, the claimed compounds are 3-4 times more active than the compounds tested, including HDMAPP, in a TNF $\alpha$  release test (see paragraph 0191 and Figure 1 of the pending application). Applicants also note that the maximum level of TNF $\alpha$  is greatly improved compared to other known compounds (1800pg/ml compared to 200-1500 pg/ml, paragraph 0192), suggesting that NHDMAAPP can lead to greater absolute  $\gamma\delta$  T cell activation *in vivo* (as compared to the other compounds tested). Such an activity would not have been expected by one of ordinary skill in the art since bioisosteres of other  $\gamma\delta$  T cell activators demonstrated antagonistic activity. Thus, one of ordinary skill in the art would not have been able to predict such an improvement in the biological effect based on the cited combination of references and withdrawal of the rejection is respectfully requested.

Claims 23-26 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully assert that there is adequate written description in the subject specification to convey to the ordinarily skilled artisan that they had possession of the claimed invention.

Claim 23 has been amended to recite that Cat $^+$  represents: H $^+$ , Na $^+$ , NH $4^+$ , K $^+$ , Li $^+$ , (CH $_3$ CH $_2$ ) $_3$ NH $^+$ , lysine or any other suitable pharmaceutically acceptable cation, as suggested by the Examiner. The objection is believed to be moot. Claim 25 has been amended to recite a list of antigens, support for which is found in paragraph 0168, thus rendering this aspect of the rejection moot. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants

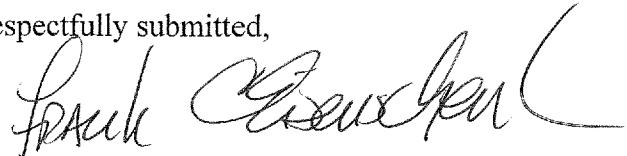
expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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